



A DIFFUSION BARRIER LAYER FOR IMPLANTABLE DEVICES

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a diffusion barrier layer for implantable devices or
5 endoluminal prostheses. More particularly the invention relates to a coating
disposed on an implantable device, one example of which includes a stent, for
inhibiting the release rate of an active ingredient carried by the device.

Description of the Background

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for
10 treating heart disease. A catheter assembly having a balloon portion is introduced
percutaneously into the cardiovascular system of a patient via the brachial or
femoral artery. The catheter assembly is advanced through the coronary
vasculature until the balloon portion is positioned across the occlusive lesion.
Once in position across the lesion, the balloon is inflated to a predetermined size to
15 radially compress against the atherosclerotic plaque of the lesion for remodeling of
the vessel wall. The balloon is then deflated to a smaller profile to allow the
catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of
intimal flaps or torn arterial linings which can collapse and occlude the conduit
20 after the balloon is deflated. Vasospasms and recoil of the vessel wall also
threaten vessel closure. Moreover, thrombosis and restenosis of the artery may
develop over several months after the procedure, which may require another

angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, an expandable, intraluminal prosthesis, one example of which includes a stent, is implanted in the
5 lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically stents are capable of being compressed, so that
10 they can be inserted through small cavities via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in the patent literature disclosing stents which have been successfully applied in PTCA procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No.
15 4,886,062 issued to Wiktor. Mechanical intervention via stents has reduced the rate of restenosis as compared to balloon angioplasty; but restenosis is still a significant clinical problem with rates ranging from 20-40%. When restenosis does occur in the stented segment, its treatment can be challenging, as clinical options are more limited as compared to lesions that were treated solely with a
20 balloon.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site,

systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

One proposed method for medicating stents disclosed seeding the stents with endothelial cells (Dichek, D.A. et al. Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; Circulation 1989; 80: 1347-1353).

Briefly, endothelial cells were seeded onto stainless steel stents and grown until

the stents were covered. The cells were therefore able to be delivered to the vascular wall where they provided therapeutic proteins. Another proposed method of providing a therapeutic substance to the vascular wall included use of a heparin-coated metallic stent, whereby a heparin coating was ionically or covalently bonded to the stent. Significant disadvantages associated with the aforementioned method includes significant loss of the therapeutic substance from the body of the stent during delivery and expansion of the stent, and an absolute lack of control of the release rate of the proteins from the stent.

Another proposed method involved the use of a polymeric carrier coated onto the surface of a stent, as disclosed in U.S. Patent No. 5,464,650 issued to Berg et al. Berg disclosed applying to a stent body a solution which included a specified solvent, a specified polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend. The solvent was allowed to evaporate, leaving

on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

Depending on the physiological mechanism targeted, the therapeutic substance may be required to be released at an efficacious concentration for an
5 extended duration of time. Increasing the quantity of the substance in the polymeric coating can lead to poor coating mechanical properties, inadequate coating adhesion, and overly fast rate of release. Increasing the quantity of the polymeric compound and producing a thicker coating can perturb the geometrical and mechanical functionality of the stent, as well as limit the procedure for which
10 the sent can be used.

It is desirable to increase the residence time of a substance at the site of implantation, at a therapeutically useful concentration, without the need for the application of a thicker coating or increasing the quantity of the therapeutic substance.

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SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, a coating for a prosthesis is provided that serves as a barrier layer. The coating contains particles. The coating can be made from a polymeric material, such as ethylene vinyl alcohol
20 copolymer. The prosthesis can be, for example, a balloon-expandable stent, a self-expandable stent, or a graft. The prosthesis can include cavities containing an active ingredient for the release of the active ingredient when the stent is implanted. Alternatively, the prosthesis can include a reservoir coating carrying an

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active ingredient. The coating containing the particles acts as a rate reducing membrane for the release of the active ingredient. In accordance with another embodiment, a primer layer which serves as an adhesive tie between the surface of the prosthesis and the reservoir coating can be provided. The reservoir coating and
5 the primer layer can be made from any suitable polymeric material such as ethylene vinyl alcohol copolymer.

In accordance with another aspect of the invention, a method of forming a coating supported by an implantable device, for example a stent, is provided. A first composition containing particles is applied to the implantable device to form a
10 coating containing the particles. The coating containing the particles acts as a rate reducing membrane for the release of an active ingredient. The coating can be made from a polymeric material such as ethylene vinyl alcohol copolymer. In accordance with one embodiment, the implantable device includes cavities containing the active ingredient. In accordance with another embodiment, prior to
15 the act of applying the first composition, a second composition containing the active ingredient is applied to the implantable device to form a reservoir coating. The reservoir coating can be a polymeric material such as ethylene vinyl alcohol copolymer. In accordance with another embodiment, a third composition can be applied to the surface of the device to form an intermediary tie layer between the
20 device and the reservoir coating.

The particles can be made from any suitable organic or inorganic material. In one embodiment, the particles are made from metals, metal oxides, carbonaceous compounds, main group oxides, nitrides, carbides, calcium salts, or

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combinations thereof. Such materials, more particularly, can include rutile titanium oxide, anatase titanium dioxide, niobium oxide, tantalum oxide, zirconium oxide, iridium oxide, tungsten oxide, silica, alumina, gold, hafnium, platinum, iridium, palladium, tungsten, tantalum, niobium, zirconium, titanium, aluminum, chromium, lamp black, furnace black, carbon black, fumed carbon black, gas black, channel black, activated charcoal, diamond, titanium nitride, chromium nitride, zirconium nitride, tungsten carbide, silicon carbide, titanium carbide, hydroxyapatite, dahlite, brushite, tricalcium phosphate, calcium sulphate, calcium carbonate, silicides, barium titanate, strontium titanate.

10 In accordance with another embodiment the particles can be made from a polymeric material such as polymers of polyolefins, polyurethanes, celluloses, polyesters, polyamides, poly(hexamethylene isophthalamide/terephthalamide), poly(ethylene terephthalate-co-p-oxybenzoate), poly(hydroxy amide ethers), polyacrylates, polyacrylonitrile, acrylonitrile/styrene copolymer, rubber-modified
15 acrylonitrile/acrylate copolymer, poly(methyl methacrylate), liquid crystal polymers, poly(phenylene sulfide), polystyrenes, polycarbonates, poly(vinyl alcohols), poly(ethylene-vinyl alcohol), epoxies composed of bisphenol A based diepoxides with amine cure, aliphatic polyketones, polysulfones, poly(ester-sulfone), poly(urethane-sulfone), poly(carbonate-sulfone), poly(3-hydroxyoxetane), poly(amino ethers), gelatin, amylose, parylene-C, parylene-D,
20 parylene-N, or combinations thereof.

Representative example of polyolefins include polyethylenes, poly (vinyl chloride), poly (vinylidene chloride), poly (vinyl fluoride), poly (vinylidene

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fluoride), poly (tetrafluoroethylene), poly (chlorotrifluoroethylene), or combinations thereof.

Representative examples of polyurethanes include polyurethanes having a glass transition temperature above physiologic temperature, or having a non-polar
5 soft segment which includes hydrocarbons, silicones, fluorosilicones, or combinations thereof.

Representative examples of cellulotics includes cellulose acetate having a degree of substitution (DS) greater than about 0.8 or less than about 0.6, ethyl
cellulose, cellulose nitrate, cellulose acetate butyrate, methyl cellulose, or
10 combinations thereof.

Representative examples of polyesters include saturated or unsaturated polyesters, including poly (ethylene terephthalate), poly(ethylene 2,6-naphthalene dicarboxylate), poly (butylene terephthalate), or combinations thereof.

Representative examples of polyamides include crystalline or amorphous
15 polyamides including nylon-6, nylon-6,6, nylon-6,9, nylon-6,10, aromatic nylon, or combinations thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A illustrates a fluid on a solid substrate having a contact angle Φ_1 ;

20 Figure 1B illustrates a fluid on a solid substrate having a contact angle Φ_2 ;

Figure 2A illustrates a diffusion barrier layer deposited over a stent in accordance with one embodiment of the present invention;

Figure 2B illustrates a diffusion barrier layer deposited over a stent in accordance with yet another embodiment of the present invention;

Figure 2C illustrates a pair of diffusion barrier layers deposited over a stent in accordance with yet another embodiment of the present invention;

5 Figure 3 graphically illustrates elution profiles for stents with a coating of ethylene vinyl alcohol copolymer impregnated with vinblastine made according to Example 4;

Figure 4 graphically illustrates in vitro experimental data, in accordance with Example 15, showing affects of actinomycin D, mitomycin, and docetaxel on
10 smooth muscle cell proliferation;

Figure 5A is a picture of a histology slide of a coronary vessel from the control group in accordance with Example 16; and

Figure 5B is a picture of a histology slide of a coronary vessel from the actinomycin D group in accordance with Example 16.

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DETAILED DESCRIPTION OF THE EMBODIMENTS

Composition for Forming an Optional Primer Layer

The embodiments of the composition for an optional primer layer are
20 prepared by conventional methods wherein all components are combined, then blended. More particularly, in accordance to one embodiment, a predetermined amount of a polymer or a prepolymer is added to a predetermined amount of a solvent or a combination of solvents. The mixture can be prepared at ambient

pressure and under anhydrous atmosphere. If necessary, a free radical or UV initiator can be added to the composition for initiating the curing or cross-linking of the prepolymer. Heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent.

5 “Polymer,” “poly,” and “polymeric” are defined as compounds that are the product of a polymerization reaction and are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, and graft variations thereof. The polymers should have a high capacity of adherence to the surface of an implantable device, such as a metallic surface of a stent. Stainless
10 steel, such as 316L, is a commonly used material for the manufacturing of a stent. Stainless steel includes a chromium oxide surface layer which makes the stent corrosion resistance and confers, in large part, biocompatibility properties to the stent. The chromium oxide layer presents oxide, anionic groups, and hydroxyl moieties, which are polar. Consequently, polymeric materials with polar
15 substituents and cationic groups can adhere to the surface. Representative examples of suitable polymeric material include polyisocyanates, unsaturated polymers, high amine content polymers, acrylates, polymers with a high content of hydrogen bonding groups, silane coupling agents, titanates and zirconates.

Representative examples of polyisocyanates include triisocyanurate,
20 aliphatic polyisocyanate resins based on hexamethylene diisocyanate, aromatic polyisocyanate prepolymers based on diphenylmethane diisocyanate, polyisocyanate polyether polyurethanes based on diphenylmethane diisocyanate,

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polymeric isocyanates based on toluene diisocyanate, polymethylene polyphenyl isocyanate, and polyester polyurethanes.

Representative examples of unsaturated polymers include polyester diacrylates, polycaprolactone diacrylates, polyester diacrylates, polytetramethylene glycol diacrylate, polyacrylates with at least two acrylate groups, polyacrylated polyurethanes, and triacrylates. With the use of unsaturated prepolymers a free radical or UV initiator can be added to the composition for the thermal or UV curing or cross-linking process. For thermal curing, examples of free radicals initiators are benzoyl peroxide; bis(2,4-dichlorobenzoyl) peroxide; dicumyl peroxide; 2,5-bis(tert-butyl peroxy)-2,5-dimethyl hexane; ammonium persulfate, and 2, 2'-azobisisobutyronitrile. As is understood by one of ordinary skill in the art, each initiator requires a different temperature to induce decomposition. For UV curing, examples of initiators include 2,2-dimethoxy-2-phenylacetophenone; 1-hydroxycyclohexyl phenyl ketone; benzoin ethyl ether; and benzophenone.

These initiators can be activated by illumination with a medium pressure Hg bulb that contains wavelengths between 250 and 350 nm.

Representative examples of high amine content polymers include polyethyleneamine, polyallylamine, and polylysine.

Representative examples of acrylates include copolymers of ethyl acrylate, methyl acrylate, butyl methacrylate, methacrylic acid, acrylic acid, and cyanoacrylates.

Representative examples of high content of hydrogen bonding group polymers include polyethylene-co-polyvinyl alcohol, epoxy polymers based on the

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diglycidylether of bisphenol A with amine crosslinking agents, epoxy polymers cured by polyols and lewis acid catalysts, epoxy phenolics, epoxy-polysulfides, ethylene vinyl acetate, melamine formaldehydes, polyvinylalcohol-co-vinyl acetate polymers, resorcinol-formaldehydes, urea-formaldehydes, polyvinylbutyral, polyvinylacetate, alkyd polyester resins, acrylic acid modified ethylene vinyl acetate polymers, methacrylic acid modified ethylene vinyl acetate polymers, acrylic acid modified ethylene acrylate polymers, methacrylic acid modified ethylene acrylate polymers, anhydride modified ethylene acrylate copolymers, and anhydride modified ethylene vinyl acetate polymers.

10 Representative examples of silane coupling agents include 3-aminopropyltriethoxysilane and (3-glycidioxypropyl) methyldiethoxysilane.

Representative examples of titanates include tetra-iso-propyl titanate and tetra-n-butyl titanate.

15 Representative examples of zirconates include n-propyl zirconate and n-butyl zirconate.

Biocompatible polymers can also be used for the primer material. Examples of biocompatible primers include poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoesters, 20 polyanhydrides, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonates), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates,

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polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-
5 alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of
10 vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose
15 acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

Ethylene vinyl alcohol is functionally a very suitable choice of polymer. The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a
20 stent without any significant detachment of the copolymer from the surface of the stent.

Ethylene vinyl alcohol copolymer, commonly known by the generic name EVOH or by the trade name EVAL®, refers to copolymers comprising residues of

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both ethylene and vinyl alcohol monomers. One of ordinary skill in the art understands that ethylene vinyl alcohol copolymer may also be a terpolymer so as to include small amounts of additional monomers, for example less than about five (5) mole percentage of styrenes, propylene, or other suitable monomers. In a
5 useful embodiment, the copolymer comprises a mole percent of ethylene of from about
27% to about 47%. Typically, 44 mole percent ethylene is suitable. Ethylene vinyl alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVAL Company of America,
10 Lisle, IL, or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art.

The solvent should be mutually compatible with the polymer and should be capable of placing the polymer into solution at the concentration desired in the solution. Useful solvents should also be able to expand the chains of the polymer
15 for maximum interaction with the surface of the device, such as a metallic surface of a stent. Examples of solvent can include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate,
20 methylethylketone, propylene glycol monomethylether, isopropanol, N-methyl pyrrolidinone, toluene and mixtures thereof.

By way of example, and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly about 2% to about 20% by weight of the

total weight of the composition, and the solvent can comprise from about 65% to about 99.9%, more narrowly about 80% to about 98% by weight of the total weight of the composition. A specific weight ratio is dependent on factors such as the material from which the implantable device is made and the geometrical structure
5 of the device.

In accordance with another embodiment, a fluid can be added to the composition to enhance the wetting of the composition for a more uniform coating application. To enhance the wetting of the composition, a suitable fluid typically has a high capillary permeation. Capillary permeation or wetting is the movement
10 of a fluid on a solid substrate driven by interfacial energetics. Capillary permeation is quantitated by a contact angle, defined as an angle at the tangent of a droplet in a fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation corresponds to a contact angle less than about 90° . Figure 1A
15 illustrates a fluid droplet 10A on a solid substrate 12, for example a stainless steel surface. Fluid droplet 10A has a high capillary permeation that corresponds to a contact angle Φ_1 , which is less than about 90° . In contrast, Figure 1B illustrates a fluid droplet 10B on solid substrate 12, having a low capillary permeation that corresponds to a contact angle Φ_2 , which is greater than about 90° . The wetting
20 fluid, typically, should have a viscosity not greater than about 5 centipoise, narrowly about 0.3 to about 5 centipoise, more narrowly about 0.4 to about 2.5 centipoise. The wetting fluid, accordingly, when added to the composition, reduces the viscosity of composition.

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The wetting fluid should be mutually compatible with the polymer and the solvent and should not precipitate the polymer. The wetting fluid can also act as the solvent. Useful examples of the wetting fluid include, but are not limited to, tetrahydrofuran (THF), dimethylformamide (DMF), 1-butanol, n-butyl acetate, 5 dimethyl acetamide (DMAC), and mixtures and combinations thereof. By way of example and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition; the solvent can comprise from about 19.9% to about 98.9%, more narrowly from about 58% to about 84% by weight of the total weight of the 10 composition; the wetting fluid can comprise from about 1% to about 80%, more narrowly from about 5% to about 40% by weight of the total weight of the composition. The specific weight ratio of the wetting fluid depends on the type of wetting fluid employed and type of and the weight ratio of the polymer and the solvent. More particularly, tetrahydrofuran used as the wetting fluid can comprise, 15 for example, from about 1% to about 44%, more narrowly about 21% by weight of the total weight of the solution. Dimethylformamide used as the wetting fluid can comprise, for example, from about 1% to about 80%, more narrowly about 8% by weight of the total weight of the solution. 1-butanol used as the wetting fluid can comprise, for example, from about 1% to about 33%, more narrowly about 9% by 20 weight of the total weight of the solution. N-butyl acetate used as the wetting fluid can comprise, for example, from about 1% to about 34%, more narrowly about 14% by weight of the total weight of the solution. Dimethyl acetamide used as the

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wetting fluid can comprise, for example, from about 1% to about 40%, more narrowly about 20% by weight of the total weight of the solution.

The presence of an active ingredient in a polymeric matrix typically interferes with the ability of the matrix to adhere effectively to the surface of the device. An increase in the quantity of the active ingredient reduces the effectiveness of the adhesion. High drug loadings of, for example, 10-40% by weight in the coating significantly hinder the retention of the coating on the surface of the device. The primer layer serves as a functionally useful intermediary layer between the surface of the device and an active ingredient-containing or reservoir coating. The primer layer provides for an adhesive tie between the reservoir coating and the device -- which, in effect, would also allow for the quantity of the active ingredient in the reservoir coating to be increased without compromising the ability of the reservoir coating to be effectively contained on the device during delivery and, if applicable, expansion of the device.

Ethylene vinyl alcohol copolymer adheres well to metallic surfaces, particularly devices made from stainless steel. The copolymer has illustrated good elastic qualities, which allow the copolymer to be delivered and, if applicable, expanded with the device without any significant detachment of the copolymer from the surface of the device.

Table 1 illustrates some examples of suitable combinations for the primer composition:

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Table 1

Polymer	Solvent	Wetting Fluid	Initiators
EVOH	DMSO	–	–
EVOH	DMSO	THF	–
polyester polyurethanes	dimethylformamid e	–	–
polyester polyurethanes	dimethylformamid e	DMAC	–
polycaprolactone	chloroform	n-butyl acetate	
polyacrylate polyurethane	ethyl acetate	–	benzophenone
polyacrylated polyurethane	ethyl acetate	–	1- hydroxycyclohexyl phenyl ketone
polyethyleneamine	H ₂ O	–	–
methacrylic acid copolymer	THF	–	–
ethylene vinylacetate (e.g., 40% vinyl acetate content)	methylethylketone	–	–
aminopropyltriethoxysilan e	ethanol/water 95/5 blend (w/w)	–	–
(3-glycidoxypropyl) methyldiethoxysilane	toluene	–	–
tetra-iso-propyl titanate (e.g., 0.25% w/w in isopropanol)	isopropanol	–	–
tetra-n-butyl titanate (e.g., 0.1-5% w/w in ethyl	ethyl acetate	–	–

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5 Composition for Forming The Active Ingredient Coating

The embodiments of the composition for an active ingredient-containing or reservoir coating are prepared by conventional methods wherein all components are combined, then blended. More particularly, in accordance to one embodiment, a predetermined amount of a polymeric compound is added to a predetermined
10 amount of a mutually compatible solvent. "Polymer," "poly," and "polymeric" are defined as a compounds that are the product of a polymerization reaction and are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, and graft variations thereof. The polymeric compound can be added to the solvent at ambient pressure and under anhydrous atmosphere. If
15 necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60° C.

Sufficient amounts of an active ingredient are dispersed in the blended composition of the polymer and the solvent. The polymer can comprise from
20 about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 59.9% to about 99.8%, more narrowly from about 79% to about 89% by weight of the total weight of the composition, and the active ingredient can comprise from about

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0.1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition. More than 9% by weight of the active ingredient could adversely affect characteristics that are desirable in the polymeric coating, such as adhesion of the coating to the device. With the use of the optional primer
5 layer, weight ratios of more than 9% for the active ingredient are achievable, without compromising the effectiveness of the adhesion. Selection of a specific weight ratio of the polymer and solvent is dependent on factors such as, but not limited to, the material from which the device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed.

10 Optionally, a second solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF) can be used to improve the solubility of an active ingredient in the composition. The second solvent can be added to the composition or the active ingredient can be added to the second solvent prior to admixture with the blend. In this embodiment, the polymer can comprise from
15 about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 19.8% to about 98.8%, usefully from about 49% to about 79% by weight of the total weight of the composition, the second solvent can comprise from about 1% to about 80%, usefully from about 5% to about 40% by weight of the total weight of
20 the composition, and the active ingredient can comprise from about 0.1% to about 40%, usefully from about 1% to about 9% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer, the solvent, and the second solvent is dependent on factors such as, but not limited to, the material

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from which the implantable device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed. The particular weight percentage of the active ingredient mixed within the composition depends on factors such as duration of the release, cumulative amount of release, and
5 release rate that is desired.

The active ingredient should be in true solution or saturated in the blended composition. If the active ingredient is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The active ingredient can also be first added to the
10 second solvent prior to admixing with the composition. The active ingredient may be added so that the dispersion is in fine particles. The mixing of the active ingredient can be conducted in an anhydrous atmosphere, at ambient pressure, and at room temperature such that supersaturating the active ingredient is not desired.

The active ingredient should inhibit the activity of vascular smooth muscle
15 cells. More specifically, the active ingredient is aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells.

“Smooth muscle cells” include those cells derived from the medial and adventitia layers of the vessel which proliferate in intimal hyperplastic vascular sites following vascular trauma or injury. Under light microscopic examination,
20 characteristics of smooth muscle cells include a histological morphology of a spindle shape with an oblong nucleus located centrally in the cell with nucleoli present and myofibrils in the sarcoplasm. Under electron microscopic examination, smooth muscle cells have long slender mitochondria in the

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juxtannuclear sarcoplasm, a few tubular elements of granular endoplasmic reticulum, and numerous clusters of free ribosomes. A small Golgi complex may also be located near one pole of the nucleus.

“Migration” of smooth muscle cells means movement of these cells in vivo
5 from the medial layers of a vessel into the intima, such as may also be studied in vitro by following the motion of a cell from one location to another, e.g., using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time.

“Proliferation” of smooth muscle cells means increase in cell number.

10 “Abnormal” or “inappropriate” proliferation means division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, i.e., hyper-proliferation.

“Inhibiting” cellular activity means reducing, delaying or eliminating
15 smooth muscle cell hyperplasia, restenosis, and vascular occlusions, particularly following biologically or mechanically mediated vascular injury or trauma or under conditions that would predispose a mammal to suffer such a vascular injury or trauma. As used herein, the term “reducing” means decreasing the intimal thickening that results from stimulation of smooth muscle cell proliferation.

20 “Delaying” means retarding the progression of the hyper-proliferative vascular disease or delaying the time until onset of visible intimal hyperplasia, as observed, for example, by histological or angiographic examination. “Elimination” of restenosis following vascular trauma or injury means completely “reducing”

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and/or completely “delaying” intimal hyperplasia in a patient to an extent which makes it no longer necessary to surgically intervene, i.e., to re-establish a suitable blood flow through the vessel by, for example, repeat angioplasty, atherectomy, or coronary artery bypass surgery. The effects of reducing, delaying, or eliminating

5 restenosis may be determined by methods known to one of ordinary skill in the art, including, but not limited to, angiography, intravascular ultrasound, fluoroscopic imaging, fiber optic visualization, optical coherence tomography, intravascular MRI, or biopsy and histology. Biologically mediated vascular injury includes, but is not limited to, injury caused by or attributed to autoimmune disorders,

10 alloimmune related disorders, infectious disorders including endotoxins and herpes viruses such as cytomegalovirus, metabolic disorders such as atherosclerosis, and vascular injury resulting from hypothermia and irradiation. Mechanical mediated vascular injury includes, but is not limited to, vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous

15 transluminal coronary angioplasty, vascular surgery, stent placement, transplantation surgery, laser treatment, and other invasive procedures which disrupted the integrity of the vascular intima or endothelium. The active ingredient of the invention is not restricted in use for therapy following vascular injury or trauma; rather, the usefulness of the active ingredient will also be

20 determined by the ingredient’s ability to inhibit cellular activity of smooth muscle cells or inhibit the development of restenosis.

The active ingredient also includes any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. The

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active ingredient can also be for enhancing wound healing in a vascular site and improving the structural and elastic properties of the vascular site. Examples of such active ingredients include antiproliferative substances as well as antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant, and combinations thereof. A suitable example of an antiproliferative substance includes actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN® available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL® (available from Squibb), CILAZAPRIL® (available from Hoffman-LaRoche), or LISINOPRIL® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast

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growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN® (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form
5 Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. Exposure of the composition to the active ingredient is not permitted to adversely alter the
10 active ingredient's composition or characteristic. Accordingly, the particular active ingredient is selected for mutual compatibility with the blended composition.

The dosage or concentration of the active ingredient required to produce a favorable therapeutic effect should be less than the level at which the active
15 ingredient produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the active ingredient required to inhibit the desired cellular activity of the vascular region can depend upon factors such as the particular circumstances of the patient; the nature of the trauma; the nature of the therapy desired; the time over which the ingredient
20 administered resides at the vascular site; and if other bioactive substances are employed, the nature and type of the substance or combination of substances. Therapeutic effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using

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immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

- 5 The polymer chosen must be a polymer that is biocompatible and minimizes irritation to the vessel wall when the device is implanted. The polymer may be either a biostable or a bioabsorbable polymer. Bioabsorbable polymers that could be used include poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate),
- 10 poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and
- 15 biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic
- 20 polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as

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polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd
5 resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

Ethylene vinyl alcohol is functionally a very suitable choice of polymer.

10 The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a stent without any significant detachment of the copolymer from the surface of the stent. The copolymer, moreover, allows for good control capabilities over the release rate of the active ingredient. As a general rule, an increase in the amount
15 of the ethylene comonomer content decreases the rate that the active ingredient is released from the matrices of the copolymer. The release rate of the active ingredient decreases as the hydrophilicity of the polymer decreases. An increase in the amount of the ethylene comonomer content decreases the hydrophilic nature of vinyl alcohol comonomer. It is also known that the release rate and the
20 cumulative amount of the active ingredient that is released is directly proportional to the total initial content of the ingredient in the copolymer's matrices.

Accordingly, a wide spectrum of release rates can be achieved by modifying the ethylene comonomer content and the initial amount of the active ingredient.

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If an optional primer layer is used, the choice of polymer for the reservoir coating can be the same as the selected polymer for the primer. The use of the same polymer significantly reduces or eliminates any interfacial incompatibilities, such as lack of adhesive tie or bond, which may exist with the employment of two
5 different polymeric layers. In effect, it can be said that the use of the same polymeric material for the primer and the reservoir coating results in the formation of a singled-layered coating.

The solvent should be capable of placing the polymer into solution at the concentration desired in the solution. Examples of solvent can include, but are not
10 limited to, DMSO, chloroform, acetone, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, and N-methyl pyrrolidinone. With the use of a low ethylene content, e.g., 29 mol%, ethylene vinyl alcohol, a suitable solvent is iso-propylalcohol (IPA) admixed with water (e.g., from about 40% to about 60%
15 by weight IPA).

Table 2 is an exemplary list of suitable combinations in accordance with various embodiment of the present invention:

Table 2

POLYMER	SOLVENT	SECOND SOLVENT	ACTIVE INGREDIENT
EVOH (29 mol% ethylene content e.g., Soarnol®)	IPA/H ₂ O (1: 1)	—	Actinomycin D
EVOH	DMSO	THF	Actinomycin D
EVOH	DMSO	DMF	Paclitaxel
poly(L-lactic acid)	chloroform	—	dexamethasone
poly(lactic acid-co-glycolic acid)	acetone	—	dexamethasone
Polyether urethane	N-methyl pyrrolidinone	—	tocopherol

5

Composition for Forming The Rate Reducing Membrane

The embodiments of the composition for a rate-reducing membrane or diffusion barrier layer are prepared by conventional methods wherein all components are combined, then dispersed. More particularly, in accordance to one embodiment, a predetermined amount of a polymeric compound is added to a

10 predetermined amount of a mutually compatible solvent. Any of the above mentioned polymers and solvents could be employed. In one embodiment, for maximum blood compatibility, polyethylene glycol or polyethylene oxide can be added to the blend.

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If an active ingredient-containing coating is employed with the practice of the present invention, the use the same polymeric compound for both the active ingredient-containing coating and the diffusion barrier layer reduces or significantly eliminates any lack of adhesion between the two layers.

5 The polymeric compound can be added to the solvent at ambient pressure and under anhydrous atmosphere. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60° C.

 Particles of inorganic or organic type are added to the blend. The particles
10 should be dispersed in the blend. Dispersed is defined as the particles being present as individual particles, not agglomerates or flocs. In certain polymer-solvent blends, certain particles will disperse with ordinary mixing. Otherwise the particles can be dispersed in the composition by high shear processes such as ball mill, disc mill, sand mill, attritor, rotor stator mixer, ultrasonication -- all such high
15 shear dispersion techniques being well known to one of ordinary skill in the art. Optionally, one of the aforementioned wetting fluids can also be added to the blend. The wetting fluid can be added prior to, contemporaneously with, or subsequent to the agitation. Biocompatible dispersing agents in the form of surfactants, emulsifiers, or stabilizers may also be added to the blend to assist in
20 particle dispersion.

 The particles can be made from any suitable material having barrier-type properties, such as, but not limited to tortuosity, excluded volume, and adsorptivity. Tortuosity refers to the exclusion of space in the polymer matrix for

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the creation of a defined space or a tortuous path through and about which the active ingredient must travel to be expelled from the layer. Excluded volume refers to the volume displaced by the particles that would otherwise be available for the diffusion of the active ingredient. Adsorptivity refers to the

5 chromatographic effect which is dependent upon the interaction between the active ingredient used in combination with the particle. The active ingredient may be partially adsorbed and released by the surface of the particles, such as silica or fumed carbon particles.

In one embodiment, the particles can be made from a metal oxide, such as
10 rutile titanium oxide, anatase titanium dioxide, niobium oxide, tantalum oxide, zirconium oxide, iridium oxide, or tungsten oxide. In another embodiment, the particles can be made from a main group oxide such as silica (silicon oxide) or alumina (aluminum oxide). Metallic particles such as gold, hafnium, platinum, iridium, palladium, tungsten, tantalum, niobium, zirconium, titanium, aluminum,
15 or chromium can also be employed. In another embodiment, carbonaceous particles made from, for example, lamp black, furnace black, carbon black, fumed carbon black, gas black, channel black, activated charcoal, diamond, diamond like carbon, or CVD diamond can be employed. In yet another embodiment, the particles can be made from nitrides such as titanium nitride, chromium nitride, and
20 zirconium nitride. In yet another embodiment, carbides such as tungsten carbide, silicon carbide, or titanium carbide, and calcium salts such as hydroxyapatite, dahlite, brushite, tricalcium phosphate, calcium sulphate, and calcium carbonate

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can be used. Other inorganic particles can include particles made from silicides, barium titanate, and strontium titanate.

In yet another embodiment, the particles can be made from a suitable polymer including polymers of polyolefins, polyurethanes, cellulosics (i.e.,
5 polymers having mer units derived from cellulose), polyesters, polyamides, poly(hexamethylene isophthalamide/terephthalamide) (commercially available as SELAR PA™), poly(ethylene terephthalate-co-p-oxybenzoate) (PET/PHB, e.g., copolymer having about 60-80 mole percent PHB), poly(hydroxy amide ethers), polyacrylates, polyacrylonitrile, acrylonitrile/styrene copolymer (commercially
10 available as LOPAC™), rubber-modified acrylonitrile/acrylate copolymer (commercially available as BAREX™), poly(methyl methacrylate), liquid crystal polymers (LCP) (e.g., VECTRA™ available from Hoescht-Celanese, ZENITE™ available from DuPont, and XYDAR™ available from Amoco Performance Chemicals), poly(phenylene sulfide), polystyrenes, polycarbonates, poly(vinyl
15 alcohols), poly(ethylene-vinyl alcohol) (EVAL®, e.g., having about 27 to about 47 mole percent of ethylene content), epoxies composed of bisphenol A based diepoxides with amine cure, aliphatic polyketones (e.g., CARILON™ available from Shell, and KETONEX™ available from British Petroleum), polysulfones, poly(ester-sulfone), poly(urethane-sulfone), poly(carbonate-sulfone), poly(3-
20 hydroxyoxetane), poly(amino ethers), gelatin, amylose, parylene-C, parylene-D, parylene-N.

Representatives polyolefins include those based upon alpha-monoolefin monomers having from about 2 to 6 carbon atoms and halogen substituted olefins,

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i.e., halogenated polyolefins. By way of example, and not limitation, low to high density polyethylenes, essentially unplasticized poly (vinyl chloride), poly (vinylidene chloride), poly (vinyl fluoride), poly (vinylidene fluoride), poly (tetrafluoroethylene) (TEFLON®), poly (chlorotrifluoroethylene) (KEL-F™), and
5 mixtures thereof are suitable. Low to high density polyethylenes are generally understood to have densities of about 0.92 g cm^{-3} to about 0.96 g cm^{-3} , however, no bright line can be drawn for density classifications and the density can vary according to the supplier.

Representative polyurethanes include polyurethanes having a glass
10 transition temperature above a storage or ambient temperature, for example having a glass transition temperature of at least 40° C to 60° C , or having a non-polar soft segment which includes a hydrocarbon, silicone, fluorosilicone, or mixtures thereof. For example, ELAST-EON™, manufactured by Elastomedic/CSIRO Molecular Science, is a polyurethane with a non-polar soft segment which is made
15 from 1,4-butanediol, 4,4'-methylenediphenyl diisocyanate, and a soft segment composed of a blend poly(hexamethylene oxide) (PHMO) and bishydroxyethoxypropylpolydimethylsiloxane (PDMS). A useful example has a blend of 20% by weight PHMO and 80% by weight PDMS.

Representative examples of cellulose include, but are not limited to,
20 cellulose acetate having a degree of substitution (DS) greater than about 0.8 or less than about 0.6, ethyl cellulose, cellulose nitrate, cellulose acetate butyrate, methyl cellulose, and mixtures thereof.

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Representative polyesters include saturated or unsaturated polyesters such as, but not limitation to, poly (butylene terephthalate), poly(ethylene 2,6-naphthalene dicarboxylate) (PEN), and poly (ethylene terephthalate).

Representative polyamides include crystalline or amorphous polyamides
5 such as, but not limited to, nylon-6, nylon-6,6, nylon-6,9, nylon-6,10, aromatic nylon MXD6 (manufactured by Mitsubishi Gas Chemical America Inc.), and mixtures thereof.

Representative polyacrylates include, but are not limited to, poly(methylmethacrylate) and polymethacrylate.

10 In one embodiment, the particle can be can be a mixture of the aforementioned polymers. For example, the polymer can comprise about 70% to about 99% by weight acrylonitrile and about 30% to about 1% by weight styrene. Similarly, copolymers of vinyl chloride and vinylidene chloride with a vinyl chloride content of about 1 to about 30 mole percent and PET/PHB copolymers
15 with a PHB content of about 60 to about 80 mole percent function effectively.

Examples of the Device

The device or prosthesis used in conjunction with the above-described compositions may be any suitable device used for the release of an active
20 ingredient, examples of which include self-expandable stents, balloon-expandable stents, stent-grafts and grafts. The underlying structure of the device can be virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY®), stainless steel

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(316L), "MP35N," "MP20N," ELASTINITE® (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof.

"MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA.

5 "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. A polymeric device should be compatible with the selected compositions. The ethylene vinyl alcohol
10 copolymer, however, adheres very well to metallic materials, such as to stainless steel.

It should be noted that the rate-reducing membrane or diffusion barrier layer in accordance with various embodiment of the present invention can be used without the active ingredient-containing coating. In this embodiment, the device
15 can include cavities or micro-pores for containing the active ingredient such that the diffusion barrier layer is disposed over the cavities. The device can be formed by sintering the stent material from metallic particles, filaments, fibers or other materials. The stent can be formed from a sintered wire that is coiled or otherwise formed into a stent. The stent can also be formed from a sintered cylindrical tube
20 or sintered metal sheet which can be laser cut or chemical etched into an expandable stent structure. Formation of cavities via sintering process is described in U.S. Patent No. 5,843,172 to Yan. By way of another example, the surface of

the device can be exposed to an etchant or a laser discharge to form cavities of selected dimensional specification.

Methods For Applying the Compositions to the Device

- 5 To form the optional primer layer and/or the active ingredient-containing coating on a surface of the device or prosthesis, the surface of the device should be clean and free from contaminants that may be introduced during manufacturing. However, the surface of the prosthesis requires no particular surface treatment to retain the applied coating. Application of the composition can be by any
- 10 conventional method, such as by spraying the composition onto the prosthesis or immersing the prosthesis in the composition. Operations such as wiping, centrifugation, blowing, or other web clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess coating from the surface of the stent; centrifugation refers to rapid rotation
- 15 of the stent about an axis of rotation; and blowing refers to application of air at a selected pressure to the deposited coating. The excess coating can also be vacuumed off the surface of the device. The addition of a wetting fluid leads to a consistent application of the composition which also causes the coating to be uniformly deposited on the surface of the prosthesis.
- 20 With the use of the thermoplastic polymers for the primer, such as ethylene vinyl alcohol copolymer, polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), etc., the deposited primer composition should be exposed to a heat treatment at temperature range greater than about the glass transition

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temperature (T_g) and less than about the melting temperature (T_m) of the selected polymer. Unexpected results have been discovered with treatment of the composition under this temperature range, specifically strong adhesion or bonding of the coating to the metallic surface of a stent. The device should be exposed to the heat treatment for any suitable duration of time, which would allow for the formation of the primer coating on the surface of the device and allows for the evaporation of the solvent or combination of solvent and wetting fluid. It is understood that essentially all of the solvent and the wetting fluid will be removed from the composition but traces or residues can remain blended with the polymer.

Table 3 lists the T_g and T_m for some of the polymers used in the embodiments of the present invention. T_g and T_m of polymers are attainable by one of ordinary skill in the art. The cited exemplary temperature and time for exposure is provided by way of illustration and it is not meant to be limiting.

Table 3

Polymer	T_g (°C)	T_m (°C)	Exemplary Temperature (°C)	Exemplary Duration of Time For Heating
EVAL®	55	165	140	4 hours
polycaprolactone	-60	60	50	2 hours
ethylene vinyl acetate (e.g., 33% vinylacetate content)	36	63	45	2 hours

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Polyvinyl alcohol	75-85*	200-220*	165	2 hours
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* Exact temperature depends on the degree of hydrolysis which is also known as the amount of residual acetate.

With the use of one of the aforementioned thermoset primer polymers, the use of initiators may be required. By way of example, epoxy systems consisting of diglycidyl ether of bisphenol A resins can be cured with amine curatives, thermoset polyurethane prepolymers can be cured with polyols, polyamines, or water (moisture), and acrylated urethane can be cured with UV light. Examples 26 and 27 provide illustrative descriptions. If baked, the temperature can be above the T_g of the selected polymer.

With the use of the inorganic primer polymers, such as silanes, titanates, and zirconates the solvent is allowed to evaporate. Example 28 provides a brief description.

The composition containing the active ingredient can be applied to a designated region of the primer coating or the surface of the device. Masking techniques can be implemented for applying compositions containing different active ingredients to selected regions of the primer layer. Accordingly, stents having various cocktail formulations or combinations of a variety of active ingredients can be manufactured. The solvent(s) or the combination of the solvent(s) and the wetting fluid is removed from the composition by allowing the solvent(s) or combination of the solvent(s) and the wetting fluid to evaporate. The evaporation can be induced by heating device at a predetermined temperature for a predetermined period of time. For example, the device can be heated at a

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temperature of about 60° C for about 12 hours to about 24 hours. The heating can be conducted in an anhydrous atmosphere and at ambient pressure and should not exceed the temperature which would adversely affect the active ingredient. The heating can, alternatively, be conducted under a vacuum condition. It is

5 understood that essentially all of the solvent and the wetting fluid will be removed from the composition but traces or residues can remain blended with the polymer.

The diffusion barrier layer can be deposited on a designated region of the active ingredient-containing coating subsequent to the evaporation of the
10 solvent(s) or solvent(s)/wetting fluid and the drying of the polymer for the active ingredient-containing coating. The diffusion barrier layer can also be applied by spraying the composition onto the device or immersing the device in the composition. The above-described processes can be similarly repeated for the formation of the diffusion barrier layer.

15

Coating

Some of the various embodiments of the present invention are illustrated by Figures 2A, 2B, and 2C. The Figures have not been drawn to scale, and the thickness of the various layers have been over or under emphasized for illustrative
20 purposes. Referring to Figure 2A, a body of a stent 20 is illustrated having surface 22. Stent 20 includes cavities or micro-pores 24 formed in the body for releasably containing an active ingredient 26, e.g., actinomycin D. A diffusion barrier layer 28 is disposed on surface 22 of stent 20, covering cavities 24. Diffusion barrier

layer 28 contains particles 30 for reducing the rate of release of active ingredient
26.

Referring to Figure 2B, stent 20 is illustrated having a primer layer 32 (e.g.,
EVOH coating) formed on surface 22. An active ingredient-containing or
5 reservoir layer 34 is deposited on primer layer 32. Primer layer 32 serves as an
intermediary layer for increasing the adhesion between reservoir 34 and surface
22. Increasing the amount of active ingredient admixed within the matrix of the
polymer diminishes the adhesiveness of reservoir layer 34 to surface 22.
Accordingly, using a substance-free polymer as an intermediary primer layer 32
10 allows for a higher active ingredient content for reservoir layer 34. Diffusion
barrier 28, having particles 30, is formed over at least a selected portion of
reservoir layer 34. One of ordinary skill in the art can appreciate that diffusion
barrier layer 28 can be deposited only on selected areas of reservoir layer 34 so as
to provide a variety of selected release parameters. Such selected patterns may
15 become useful if a combination of active ingredients are used, each of which
requires a different release parameter.

Figure 2C illustrates stent 20 having a first reservoir layer 34A disposed on
a selected portion of surface 22 of stent 20. First reservoir layer 34A contains a
first active ingredient, e.g., actinomycin D. A second reservoir layer 34B can also
20 be disposed on surface 22. Second reservoir layer 34B contains a second active
ingredient, e.g., taxol. First and second reservoir layers 34A and 34B are covered
by first and second diffusion barrier layers 28A and 28B, respectively. Such
selective patterning can be achieved by, for example, masking the designated

regions prior to the application of the composition. In accordance with one embodiment, more particles are deposited in the polymer for diffusion barrier layer 28B. Accordingly, the packing density or particle volume fraction for diffusion barrier layer 28B is greater than the packing density for diffusion barrier layer 28A. Packing density or particle volume fraction can be defined by the following equation:

$$X_p = V_{\text{particles}} / (V_{\text{particles}} + V_{\text{polymer}})$$

wherein V is volume.

Alternatively, for a higher packing density, particles 30B can, for example, be of greater size than particles 30A. In accordance with yet another embodiment, the polymeric material from which diffusion barrier layer 28A is made can be different than the material from which diffusion barrier layer 28B is made. Accordingly, a wide array of release parameters can be obtained for any selected combination of active ingredients.

Diffusion barrier layer 28 can have any suitable thickness, as the thickness of diffusion barrier layer 28 is dependent on parameters such as, but not limited to, the desired rate of release and the procedure for which the stent will be used. Diffusion barrier layer 28 can have a thickness of about 0.1 to about 10 microns, more narrowly from about 0.25 to about 2 microns. For a smooth surface, the size of particles 30 should not be greater than about 10% of the thickness of diffusion barrier layer 28. Additionally, the particle volume fraction X_p should not exceed about 0.74.

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By way of example, and not limitation, the impregnated reservoir layer 34 can have a thickness of about 0.5 microns to about 1.5 microns. The particular thickness of reservoir layer 34 is based on the type of procedure for which stent 20 is employed and the amount of the active ingredient that is desired to be delivered.

- 5 The amount of the active ingredient to be included on the prosthesis can be further increased by applying a plurality of reservoir layers 34 on top of one another. The optional primer layer 32 can have any suitable thickness, examples of which can be in the range of about 0.1 to about 10 microns, more narrowly about 0.1 to about 2 microns.

10

Method of Use

- In accordance with the above-described method, the active ingredient can be applied to a device, e.g., a stent, retained on the stent during delivery and expansion of the stent, and released at a desired control rate and for a
- 15 predetermined duration of time at the site of implantation. A stent having the above-described coating layers is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating layers is particularly useful for treating
- 20 occluded regions of blood vessels caused abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries.

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Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by injecting a radiopaque contrast agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described coating layers may then be expanded at the desired area of treatment. A post insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

The embodiments of the invention will be illustrated by the following set forth examples which are being given by way of illustration only and not by way of limitation. All parameters and data are not be construed to unduly limit the scope of the embodiments of the invention.

Example 1

MULTI-LINK® stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH

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solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60° C for 24 hours. The solution was cooled and vortexed. The cleaned MULTI-LINK® stents were dipped in the EVOH solution and then passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were heated for 6 hours in an air box and then placed in an oven at 60° C, under vacuum condition, and for 24 hours. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. The coatings were transparent giving the MULTI-LINK® stents a glossy-like shine.

Example 2

MULTI-LINK® stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 4 grams of DMSO, making an EVOH: DMSO ratio of 1:4. Dexamethasone was added to the 1:4 EVOH: DMSO solution. Dexamethasone constituted 9% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned MULTI-LINK® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box and then placed in a vacuum oven at 60° C for 24 hours. The above-recited step was repeated twice. The

average weight of the coating was 0.0003 gram, having an estimated dexamethasone content of 75 ug per stent. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. Verification of coverage and physical properties of the coatings were visualized using a scanning electron microscope. The coatings were transparent, giving the MULTI-LINK® stents a glossy-like shine.

Example 3

MULTI-LINK DUET® stents are cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents are dried and plasma cleaned in a plasma chamber. The EVOH solution is made with 1 gram of EVOH and 4 grams of DMSO, making an EVOH: DMSO ratio of 1:4. Dexamethasone is added to the 1:4 EVOH: DMSO solution. Dexamethasone constitutes 9% by weight of the total weight of the solution. The solution is vortexed and placed in a tube. The cleaned MULTI-LINK® stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents are cured for 6 hours in an air box then placed in a vacuum oven at 60° C for 24 hours. The single layered dexamethasone/EVOH coated stents are dipped into the 1:4 ratio EVOH:DMSO solution, free from dexamethasone. The stents are passed over the hot plate, cured, and placed in the oven as previously described. The top coating will provide a barrier layer for controlling the release of dexamethasone from the drug coated layer. The coated stents can be expanded on a 4.0 mm angioplasty

balloon. It is predicted that the coatings will remain intact on the stents. The coatings will be transparent, giving the MULTI-LINK® stents a glossy-like shine.

5

Example 4

MULTI-LINK® stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. Vinblastine
10 was added to the 1:7 EVOH:DMSO solution. Vinblastine constituted 2.5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned MULTI-LINK® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were
15 cured for 6 hours in an air box then placed in a vacuum oven at 60° C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00005 gram, with an estimated vinblastine concentration of 12 microgram per stent. Some of the stents were sterilized by electron beam radiation. The sterilized and unsterilized vinblastine coated stents
20 were tested for a 24 hour elution period by placing one sterilized and one unsterilized stent in 5 ml of phosphated saline solution (pH 7.4) at room temperature with rotational motion. The amount of vinblastine eluted was evaluated by High Performance Liquid Chromatography (HPLC) analysis. The

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results of this test are given below in Tables 4A and 4B and plotted in Figure 3.

The data indicates that electron beam radiation procedure does not interfere in the release of vinblastine from EVOH.

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Table 4A

Release Profile For Vinblastine -- Unsterilized

Time (Hours)	microgram Released	Total microgram Released	microgram Release per Hour
0	0	0	0
0.5	2.12	2.12	4.24
3	1.91	4.03	0.76
4	0.27	4.30	0.27
6	0.38	4.68	0.19
24	1.7	6.38	0.09

5

Table 4B

Release Profile For Vinblastine -- Sterilized

Time (Hours)	ug Release	Total uG Released	uG Release per Hour
0	0	0	0
0.5	2.14	2.14	4.28
3	1.7	3.84	0.68
4	0.28	4.12	0.28
6	0.26	4.38	0.13
24	2.05	6.43	0.11

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Example 5

MULTI-LINK® stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma
5 cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. Cephalotaxin was added to the 1:7 EVOH: DMSO solution. Cephalotaxin constituted 5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned MULTI-LINK® stents were attached
10 to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60° C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00013 gram, with an estimated
15 cephalotaxin concentration of 33 ug. The stents were sterilized by electron beam radiation. Cephalotaxin/EVOH coated stents and EVOH-coated control stents were implanted in the coronary arteries of 4 pigs, generally in accordance to the procedure set forth in "Restenosis After Balloon Angioplasty-A Practical Proliferative Model in Porcine Coronary Arteries" by Robert S. Schwartz, et al.,
20 Circulation 82(6):2190-2200, Dec. 1990, and "Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model" by Robert S. Schwartz et al, J Am Coll Cardiol; 19:267-74 Feb. 1992. Results of the porcine artery study indicated that there was no significant difference between the

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uncoated, EVOH coated and cephalotaxin coated stents in the amount of neointimal proliferation resulting from arterial injury.

Example 6

5 MULTI-LINK DUET® stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 20 minutes, then air dried. An EVOH stock solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was
10 mixed, then cooled to room temperature. A co-solvent was added to the EVOH solution to promote wetting of the struts of the MULTI-LINK DUET® stents. One gram of tetrahydrofuran (THF) was mixed with 1.2 grams of the EVOH: DMSO solution. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate,
15 for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were then heated in a laboratory oven at 90° C for 4 hours. The thin EVOH coating adhered to stainless steel without peeling or cracking. EVOH forms a superior primer base coat for other polymers that do not adhere well to stainless steel.

20

Example 7

MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH solution was made

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with 1 gram of EVOH and 5 grams of DMSO, making an EVOH: DMSO ratio of 1:5. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. The dissolved EVOH: DMSO solution was mixed with 24.6 grams of THF and 19.56 grams of DMSO.

5 The solution was mixed then placed in the reservoir of an air pressured atomizing sprayer. MULTI-LINK DUET® stents were sprayed while the stents rotated between 30 to 120 rpm. The spray time was dependent upon the flow rate of the sprayer. A flow rate between 1 to 20 mg/second required a stent to be sprayed between 1 to 30 seconds. The polymer coated MULTI-LINK DUET® stents were

10 heated in a forced air convection oven for 12 hours. The coatings were transparent, giving the MULTI-LINK DUET® stents a glossy-like shine.

Example 8

MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of

15 isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. Various co-solvents were examined to determine which co-solvent would promote a thicker coating. These co-solvents were THF, DMF, 1-

20 butanol, and n-butyl acetate. The formulation for the co-solvents was as follows. Three grams of dissolved EVOH: DMSO solution was mixed with 0.9 gram of THF; three grams of dissolved EVOH: DMSO solution was mixed with 0.39 gram of DMF; three grams of dissolved EVOH: DMSO solution was mixed with 0.5

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gram of 1-butanol; and three grams of dissolved EVOH: DMSO solution was mixed with 0.68 gram of n-butyl acetate. The cleaned MULTI-LINK DUET® stents, attached to mandrel wires, were dipped into the solutions. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were heated in a forced air convection oven for 24 hours. A second layer of coating was applied to coated MULTI-LINK DUET® stents and the stents were heated in the same manner as above. No difference was seen between the stents coated with the various co-solvents (e.g., greater weight of coating or physical appearance). All coated stents were transparent, giving the MULTI-LINK DUET® stents a glossy-like shine. No webbing or bridging of the coating was seen between the struts of the coated MULTI-LINK DUET® stents. The weight of the coatings was between 0.2 to 0.27 mg/stent.

15

Example 9

MULTI-LINK DUET® stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH: DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVOH: DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned MULTI-LINK DUET® stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a

20

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hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the MULTI-LINK DUET® stents a glossy-like shine.

Example 10

MULTI-LINK DUET® stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH: DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVOH: DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned MULTI-LINK DUET® stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the MULTI-LINK DUET® stents a glossy-like shine.

Example 11

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MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 4.75% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVOH: DMSO solution was mixed with 40 milligrams of actinomycin D, then 200 milligrams of THF was added. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 12

MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 3.60% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVOH: DMSO solution was mixed with 40 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5

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seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

5

Example 13

MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.45% by weight actinomycin D solution was formulated as follows: 680 milligrams of the EVOH: DMSO solution was mixed with 80 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

20

Example 14

MULTI-LINK DUET® stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH: DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath

at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A
0.60% by weight actinomycin D solution can be formulated as follows: 4920
milligrams of the EVOH: DMSO solution is mixed with 40 milligrams of
Actinomycin D, then 2000 milligrams of THF is added. The cleaned MULTI-
5 LINK DUET® stents can be sprayed upon by the above formulation. The coated
stents are cured in a forced air convection oven for 2 hours. A second layer of
coating is applied and cured in the above manner.

Example 15

10 Inhibition of SMC proliferation with Actinomycin D

Medial smooth muscle cells (SMC) were isolated from rat aorta and
cultured according to explant methods known to one of ordinary skill in the art.
Cells were harvested via trypsinization and subcultivated. Cells were identified as
vascular SMC through their characteristic hill-and-valley growth pattern as well as
15 indirect immunofluorescence with monoclonal anti SMC α -actin. Studies were
performed with cells at passage 3-4. SMC monolayers were established on 24 well
culture dishes, scrape wounded and treated with actinomycin D, mitomycin and
docetaxel. The cells were exposed to the drug solution of different concentrations
for 2 hours and then washed with buffered saline solution. The proliferation of the
20 cells was quantified by standard technique of thymidine incorporation. The results
from the study are tabulated in Figure 4.

The IC₅₀ (concentration at which 50% of the cells stop proliferating) of
actinomycin D was 10⁻⁹M as compared to 5 x 10⁻⁵M for mitomycin and 10⁻⁶M

for docetaxel. Actinomycin D was the most potent agent to prevent SMC proliferation as compared to other pharmaceutical agents.

5

Example 16

Reduction in Restenosis in the Porcine Coronary Artery Model

Porcine coronary models were used to assess the degree of the inhibition of neointimal formation in the coronary arteries of a porcine stent injury model by
10 Actinomycin D, delivered with a microporous balloon catheter (1×10^6 pores/mm² with sizes ranging from 0.2-0.8 micron).

The preclinical animal testing was performed in accordance with the NIH Guide for Care and Use of Laboratory Animals. Domestic swine were utilized to evaluate effect of the drug on the inhibition of the neointimal formation. Each
15 testing procedure, excluding the angiographic analysis at the follow-up endpoints, was conducted using sterile techniques. During the study procedure, the activated clotting time (ACT) was monitored regularly to ensure appropriate anticoagulation. Base line blood samples were collected for each animal before initiation of the procedure. Quantitative coronary angiographic analysis (QCA)
20 and intravascular ultrasound (IVUS) analysis was used for vessel size assessment.

The vessels at the sites of the delivery were denuded by inflation of the PTCA balloons to 1: 1 balloon to artery ratio and moving the balloons back and forth 5 times. The drug was delivered to the denuded sites at 3.5 atm (3.61 Kg/sq

Substitute Specification

cm) for 2 minutes using the microporous balloon catheters before stent deployment. The average volume of delivery was about 3.3 +/- 1.2 ml. Following drug delivery, stents were deployed at the delivery site such that final stent to artery ratio was 1.1: 1.

5 QCA and IVUS analyses were used for stent deployment guidance. Pre-stenting IVUS measurements of the lumen size at the targeted vessel sites were performed for determination of the balloon (size) inflation pressure. Quantitative analysis of the stented coronary arteries to compare pre-stenting, post-stenting, follow-up minimal luminal diameters, stent recoil, and balloon/stent to artery ratio
10 were performed. Following stent implantation and final angiogram, all devices were withdrawn and the wounds closed; the animals were allowed to recover from anesthesia as managed by the attending veterinarian or animal care professionals at the research center.

 Upon return to the research laboratory at the 28-day endpoint, angiographic
15 assessments were performed. Coronary artery blood flow was assessed and the stented vessels were evaluated to determine minimal lumen diameter. The animals were euthanized following this procedure at the endpoint. Following euthanasia, the hearts were pressure perfusion fixed with formalin and prepared for histological analysis, encompassing light microscopy, and morphometry.
20 Morphometric analysis of the stented arteries included assessment of the position of the stent struts and determination of vessel/lumen areas, percent (%) stenosis, injury scores, intimal and medial areas and intima/media ratios. Percent stenosis is quantitated by the following equation:

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$$100 (\text{IEL area} - \text{lumen area}) / \text{IEL area}$$

where IEL is the internal elastic lamia.

The control group of animals received delivery of water instead of the drug.

The test group of animals received actinomycin D in two different concentration of
 5 10^{-5}M and 10^{-4}M . The results of the study are tabulated in Table 5. The percent
 stenosis in the treated groups (32.3 ± 11.7) was significantly decreased as
 compared to the control groups (48.8 ± 9.8). Figures 5A and 5B illustrate sample
 pictures of the histology slides of the coronary vessels from the control and the
 Dose 1 group, respectively.

10

Table 5

	CONTROL	DOSE 1	DOSE 2	t test (significant if $p < 0.05$)	
	0M	1E-05M	1E-04M		
	(n=9)	(n=10)	(n=7)	p~	p*
ANGIOGRAPHIC DATA (QCA)					
Percent Diameter	48.8 +/- 9.8	36.8 +/- 9.7	32.3 +/- 11.7	0.02	0.01
Stenosis					

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	CONTROL	DOSE 1	DOSE 2	t test (significant if $p < 0.05$)	
	0M	1E-05M	1E-04M		
	(n=27)	(n=30)	(n=21)	p~	p*
HISTOMORPHOMETRIC DATA					
Percent Stenosis (IEL area-lumen area)/IEL area	63.4 +/- 12.7	51.8 +/- 13.8	54.1 +/- 11.7	0.002	0.01
Residual Lumen (Lumen area)/IEL area	0.36 +/- 0.16	0.49 +/- 0.14	0.46 +/- 0.08	0.002	0.01

~ comparison between control and Dose 1

* comparison between control and Dose 2

- The results of the in vitro and in vivo standard test procedures
- 5 demonstrate that actinomycin D is useful for the treatment of hyper-proliferative vascular disease. Specifically, actinomycin D is useful for the inhibition of smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly occlusions following a mechanically mediated vascular trauma or injury.

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MULTI-LINK DUET® stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was

5 mixed, then cooled to room temperature. A 5.06% by weight actinomycin D solution was formulated as follows: 40 milligrams of actinomycin D was dissolved in 150 milligrams of THF, then 600 milligrams of the EVOH: DMSO was added. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about

10 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C for 4 hours. An average coating weight of about 260 micrograms and an average actinomycin D loading of about 64 micrograms was achieved.

15

Example 18

MULTI-LINK DUET® stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was

20 placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 3.75% by weight actinomycin D solution was formulated as follows: 60 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVOH: DMSO solution was added.

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The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C for 1 hour. A second layer of
5 coating was applied in the above manner and cured in a forced air convection oven at 60° C for 4 hours. An average coating weight of about 270 micrograms with an average actinomycin D content of about 51 micrograms was achieved.

Example 19

10 MULTI-LINK DUET® stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.1% by weight actinomycin D solution was formulated as
15 follows: 100 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVOH: DMSO was added. The cleaned MULTI-LINK DUET® stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air
20 convection oven at 60°C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C for 4 hours. An average coating weight of about 250 micrograms and an average actinomycin D loading of about 75 micrograms was achieved.

Example 20

MULTI-LINK DUET® stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an
5 EVOH: DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVOH: DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned MULTI-
10 LINK DUET® stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven 60° C for 15 minutes. Additional layers of the coating are applied and cured in the above manner. The final curing step for the coated stents is conducted for about 4 hours.

15

Example 21

A stainless steel stent can be spray coated with a formulation of EVAL® and a drug, as previously described in any of the above examples. A diffusion barrier composition can be formulated with 2 grams of EVAL® blended with 20 grams of dimethylsulfoxide. 2.2 grams of fumed silica can be
20 added and dispersed with a high shear process. With constant agitation, 50 grams of tetrahydrofuran and 30 grams of dimethylformamide are admixed with the blend. The stent, having the EVAL® coating, can be immersed in the diffusion barrier composition to form a layer.

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Example 22

A stainless steel stent can be spray coated with a formulation of EVAL® and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVAL® into 32 grams of dimethylsulfoxide. To this is added 14 grams of rutile titanium dioxide and 7 grams more of dimethylsulfoxide. The particles can be dispersed using a ball mill. The final solution is diluted with 39 grams of tetrahydrofuran, added slowly with constant agitation. It is predicted that the diffusion barrier will reduce the rate at which the drug is released from the stent.

Example 23

A stainless steel stent can be coated with a formulation of EVAL® and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVAL® in 32 grams of dimethylsulfoxide. 10.5 grams of solution precipitated hydroxyapatite can be added to the blend. The particles can be dispersed using a rotor stator mixer. With constant agitation, 30 grams of tetrahydrofuran can be added. The stent can be coated by immersion followed by centrifugation.

20

Examples 24

A stent can be coated with a formulation of EVAL® and a drug, as previously described in any of the above examples. 8 grams of EVAL® can be

Substitute Specification

added 50 grams of dimethylsulfoxide and the polymer can be dissolved by agitation and heat. Four grams of lamp black can be added and dispersed in a ball mill. 60 grams of dimethyl sulfoxide and 110 grams of tetrahydrofuran are slowly added while stirring. The stent can be spray coated.

5

Example 25

A stent can be coated with a formulation of EVAL® and a drug, as previously described in any of the above examples. Colloidal gold can be prepared by reduction of tetrachloroauric acid with sodium citrate in aqueous solution. The solution can be exchanged by rinsing with tetrahydrofuran. Eight grams of EVAL® can be dissolved in 32 grams of dimethylsulfoxide. To this is added a solution of 77 grams of colloidal gold in 32 grams of tetrahydrofuran. The stent can be coated by a dip coating process.

15

Example 26

2 grams of an acrylate terminated urethane (HENKEL® 12892) can be added to 18 grams of ethyl acetate with 0.08 grams of benzophenone and 0.08 grams of 1-hydroxycyclohexyl phenyl ketone. After application, the stent can be cured for 5 minutes under medium pressure mercury lamp.

20

Example 27

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For a thermoset system, 1.67 grams of EPON® 828 (Shell) resin can be added to 98 grams of propylene glycol monomethyl ether and 0.33 grams of JEFFAMINE® T-430 (Huntsman). After application, the stent can be baked for 2 hours at 80°C and 2 hours at 160°C.

5

Example 28

A 0.25% (w/w) solution of tetra-n-butyl titanate can be made in anhydrous ethyl acetate. The solution can be applied by spraying to a surface of a stainless steel stent. The stent can be heated at 100°C for two hours.

10

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this

15

invention.